

REMARKS

Claims 1-67 are currently pending in the application. Claims 1-22 are under consideration (23-67 having been withdrawn as drawn to non-elected subject matter). By the present communication, claims 1, 3, 12, and 14 have been amended and new claims 68-73 have been added. The amended claim language is supported throughout the as-filed specification for example, at paragraph [0081], the Examples, and in the claims as filed. No new matter has been added. In view of these amendments, claims 4 and 15 have been canceled without prejudice or disclaimer. After entry of the present amendment, claims 1-3, 5-14, 16-22, 68-73 will be under consideration.

Priority

The Examiner asserts that the present claims are not entitled to the benefit of priority to Application No. 60/487,554 (hereinafter “the ‘554 application”), filed July 15, 2003, and instead are only entitled to benefit of International Patent No. PCT/US04/22698, filed on July 15, 2004. Applicants respectfully disagree.

Applicants respectfully submit that the present claims are supported by the ‘554 application. Applicants note that the figures supplied in the ‘554 application disclose essentially the same data as the figures in Berman *et al.* (*Nature* 425:846, 2003; hereinafter “Berman”), which the Examiner has cited in a rejection of claims 1-3, 5-7, 10-14, 16, 18, and 21-22 under 35 U.S.C. §102(a). Applicants submit that the Examiner’s assertion that the claims are anticipated by this reference is an acknowledgment that these claims are supported by the ‘554 provisional application, which includes essentially the same disclosure as Berman *et al.* Accordingly, Applicants submit that, at a minimum, claims 1-3, 5-7, 10-14, 16, 18, and 21-22 are entitled to benefit of priority to the filing date of the ‘651 provisional application.

Rejections Under 35 U.S.C. §102

Claims 1-3, 5-7, 10-14, 16, 18 and 21-22 stand rejected under 35 U.S.C. §102(a), as allegedly being anticipated by Berman *et al.* (*supra*). Applicants respectfully traverse the rejection.

The Examiner asserts that Berman discloses the suppression of the Hh pathway in esophagus, stomach, biliary, and pancreatic tumor cells by cyclopamine *in vitro* and *in vivo*.

Applicants submit that Berman is not available as prior art under 35 U.S.C. §102(a). As discussed above, the present claims are entitled to claim the benefit of priority of the '554 provisional application, filed July 15, 2003. Berman, which cites a publication date of October 23, 2003, was published some three months *after* the priority date. Thus, Berman fails to meet the standard under 35 U.S.C. §102(a), in which the reference must have been described in a printed publication before the date of invention. Accordingly, Berman is not available as prior art under 35 U.S.C. §102(a).

Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-10 and 12-21 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Ling *et al.* (U.S. Patent Publication No.: 2003/0022819; hereinafter "Ling"). Applicants respectfully traverse the rejection.

The Examiner alleges that Ling teaches methods and reagents for the inhibition of undesired growth states that occur in cells with an active hedgehog signaling pathway, including gastrointestinal tumors. The Examiner further alleges that Ling teaches hedgehog pathway antagonists including antibodies. Applicants respectfully disagree and submit that Ling does not anticipate the present claims because the disclosure of Ling does not enable the presently claimed methods.

The present invention, as defined by, for example claim 1, relates to a method of reducing or inhibiting metastasis of cells of a metastatic digestive tract tumor characterized by abnormally

elevated Hedgehog (Hh) pathway activity, by contacting the cells with at least one Hh pathway antagonist, thereby reducing or inhibiting proliferation of the cells of the digestive tract tumor, wherein the cells are pancreatic cancer cells, stomach cancer cells, esophagus cancer cells, or biliary tract cancer cells.

According to the Federal Circuit, the disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003). Applicants respectfully submit that Ling does not provide an enabling disclosure for the present methods of reducing or inhibiting metastasis of the cells of a digestive tract tumor, wherein the cells are pancreatic cancer cells, stomach cancer cells, esophagus cancer cells or biliary tract cancer cells, or methods of ameliorating such cancers in a subject, using a Hh signaling pathway antagonist. Indeed, Ling provides no teaching with regard to the direct effect of hedgehog pathway antagonists on pancreatic, stomach, esophagus or biliary tract cancer cells, much less any *in vitro* or *in vivo* examples of such effects.

Applicants respectfully submit that the disclosure of Ling is directed to hedgehog signaling in angiogenesis, as well as certain proliferative disorders derived from different cell types. However, the skilled artisan would recognize that the behavior of a compound in one type of cell, does not necessarily predict the behavior of that compound in another type of cell, let alone a cancer cell. Thus, Ling provides little in the way of guidance and no working examples of a method to reduce or inhibit proliferation or metastasis of pancreatic, stomach, esophagus or biliary tract cancer cells using a Hh pathway antagonist. Therefore, Applicants submit that one of ordinary skill in the art would require inventive effort amounting to undue experimentation, to practice the presently claimed invention in view of Ling.

Anticipation under 35 U.S.C. §102(b) requires that the reference recite each and every element of the claims in a single document, and that the single document provide an enabling disclosure of the full scope of the claimed invention. Because Ling fails to enable the methods of the claimed invention, Applicants respectfully submit that the Examiner has failed to establish

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anticipation under 35 U.S.C. §102 (b) over Ling. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-3, 7, 10-14, 18 and 21-22 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Beachy *et al.* (PCT Patent Publication No.: WO 01/27135; hereinafter “Beachy”). Applicants respectfully traverse the rejection.

The Examiner asserts that Beachy discloses molecules that counteract the phenotypic effects of unwanted activation of the hedgehog signaling pathway. The Examiner further asserts that the molecules are small molecules and that the diseases to be treated include pancreatic and gastrointestinal tumors. Applicants respectfully submit, however, that Beachy does not teach all of the elements of the presently amended claims.

In particular, Applicants respectfully submit that Beachy does not teach a method of reducing or inhibiting metastasis of the cells of a metastatic digestive tract tumor, wherein the cells are pancreatic cancer cells, stomach cancer cells, esophagus cancer cells or biliary tract cancer cells, or methods of ameliorating such cancers in a subject, using a Hh signaling pathway antagonist. Indeed, Beachy provides no experimental data demonstrating the direct effect of hedgehog pathway antagonists on pancreatic, stomach, esophagus or biliary tract cancer cells. Further, Beachy is silent with regard to the role of hedgehog signaling in metastasis of such tumors. Thus, Applicants respectfully submit that Beachy does not anticipate the presently claimed methods. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-22 stand rejected under 35 U.S.C. §102(e), as allegedly being anticipated by Dudek *et al.* (U.S. Patent Publication No.: 2004/0060568; hereinafter “Dudek”). Applicants respectfully traverse the rejection as it applies to the pending claims.

The Examiner alleges that Dudek teaches methods and reagents for the inhibition of undesired growth states that occur in cells with an active hedgehog signaling pathway. The

Examiner further alleges that Dudek teaches hedgehog pathway antagonists including antibodies and cyclopamine. Applicants respectfully disagree and submit that Dudek does not anticipate the present claims because the disclosure of Dudek does not enable the presently claimed methods.

In particular, Applicants respectfully submit that Dudek does not enable the presently claimed methods of reducing or inhibiting metastasis of pancreatic cancer cells, stomach cancer cells, esophagus cancer cells or biliary tract cancer cells, or methods of ameliorating such cancers in a subject, using a Hh signaling pathway antagonist. Indeed, Dudek provides no teaching with regard to the direct effect of hedgehog pathway antagonists on pancreatic, stomach, esophagus, or biliary tract cancer cells, much less any *in vitro* or *in vivo* examples of such effects.

In addition, the disclosure of Dudek is directed to hedgehog signaling in lung cell development and stimulation of surfactant release, as well as certain proliferative disorders derived from different cell types. However, the skilled artisan would recognize that the behavior of a compound in one type of cell, does not necessarily predict the behavior of that compound in another type of cell, let alone a cancer cell. Thus, Dudek provides little in the way of guidance and no working examples of a method to reduce or inhibit proliferation or metastasis of pancreatic, stomach, esophagus, or biliary tract cancer cells using a Hh pathway antagonist. Therefore, Applicants submit that one of ordinary skill in the art would require inventive effort and undue experimentation to practice the presently claimed invention in view of Dudek.

Anticipation under 35 U.S.C. §102(e) requires that the reference recite each and every element of the claims in a single document, and that the single document provide an enabling disclosure of the full scope of the claimed invention. Because Dudek fails to enable the methods of the presently claimed invention, Applicants respectfully submit that the Examiner has failed to establish anticipation under 35 U.S.C. §102(e) over Dudek. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

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CONCLUSION

If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Please charge \$104.00 to Deposit Account No. 07-1896 to cover the extra claims fees, small entity, for four (4) additional claims pending in the present application. No other fee is believed to be due in connection with the submission filing of this paper. However if any additional fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

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